Improving the regulation and social acceptance of crop-protection and seeds products produced using new technologies

Improving the regulation and social acceptance of crop-protection and seeds products produced using new technologies: an industry perspective

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Introduction

Many practices in agriculture are regulated and must be approved by statutory authorities before they can be undertaken legally. Regulation is intended to ensure that risks from agriculture to human and animal health and to the environment are kept to an acceptable level. The acceptability of risk may be judged relative to the potential benefits of the practice or against an absolute standard. Among regulated activities are the use of synthetic chemical crop-protection products (pesticides[1]) (Handford et al. 2015) and genetically engineered (GE) seeds (McHughen 2012). Use of biological pesticides, such as pathogens of crop pests, and seeds produced without using genetic engineering ("conventional" seeds) are also regulated in many countries.

Regulatory approvals are granted for specific uses of individual products over a limited time. An approval to use a given crop-protection product may stipulate many conditions, including the permitted crops and application methods, the maximum amount of the product that may be applied, restrictions on the number, timing and sites of application, and any protective equipment that must be worn while using the product (Müller et al. 2014). Conditions for use of GE seeds may restrict where they are grown in order to limit cross-fertilisation with non-GE crops (Devos *et al*. 2009) or, in the case of insect-resistant crops, to delay the evolution of resistance in the targeted pests (Tabashnik 2013).

Whether the use of a product is regulated, and the form any regulation takes, often depends on the process by which the product is produced rather than on the effect it intended to achieve. Such "process-based" regulation can lead to products with similar properties being treated very differently. The replacement of synthetic chemical pesticides by biological pesticides, for example, is encouraged in many countries, and leads to decision-making over biological pesticides being simpler and quicker than for synthetic pesticides (Balog et al. 2017). This is the case despite some biological pesticides being less well characterised and having greater ability to persist and spread in the environment than is the case for synthetic pesticides (Chandler et al. 2008).

Similar situations are found in the seed industry. The main reason for regulating the use of conventional seeds is protection of plant breeders' rights (Brahmi and Chaudhary 2011); therefore, regulation focuses on whether a new conventional variety is distinct from older varieties, as well as its being uniform and stable (Yan et al. 2015), rather than whether use of the new variety poses unacceptable risk. Thus, there is no pre-market regulatory requirement to assess the risks to human health and the environment from, say, the cultivation of a herbicide-tolerant crop produced by conventional breeding – although its developers may choose to conduct such an assessment for their own purposes. An extensive risk assessment would be required in order to commercialise a GE crop designed to be tolerant to the same herbicide (Hérouet *et al*. 2005). An exception is Canada, where regulatory risk assessment for seeds is triggered by their possessing a trait that is new to the species,

[1] Strictly, a pesticide is a substance that controls any pest; a crop-protection or plant-protection product is a formulation of a pesticide designed to control pests of crops

regardless of how that new trait was produced (Macdonald 2014); this is an example of "product-based" regulation.

Regulation imposes significant costs on the developers of regulated products and on society generally. The cost of developing a new synthetic pesticide was estimated recently to be US $286 million, a 55% increase since 2000 when the cost was US $184 million. Roughly 12% of the development cost is for pesticide registration; however, a further 25% is for toxicology and environmental chemistry studies that comprise much of the evidence to support applications to register product uses (Sparks and Lorsbach 2017). The increasing cost of development, along with less predictability in regulatory decision-making, means that fewer companies can develop new pesticides and that new products are targeted at large markets in order to recoup the costs of development. These trends inevitably lead to less innovation targeted at small, niche markets (Maienfisch and Stevenson 2015). The consequences of these economic pressures are uncertain. However, one is likely to be less diversity in cropping systems if products that allowed the economic production of certain crops become obsolete and cannot be replaced. Lower diversity may lead to greater vulnerability to environmental changes such as the evolution of new pests and pathogens.

Use of crop-protection products provides numerous benefits to human wellbeing. Potential loss of crop yield to damage by pests is estimated to be 50–80% by crop, but actual losses are about 25–40% owing to the use of control methods that include pesticides (Oerke and Dehne 2004). Reducing yield losses has many associated benefits, including increased food security and safety, improved livelihoods for farmers and reducing pressure to cultivate more land (Cooper and Dobson 2007). Maintaining and extending these benefits is a key aim of research and development (R&D) in the crop-protection industry. A second, and equally important, aim is to reduce or eliminate harmful side-effects resulting from the use or misuse of crop-protection products. An ideal pesticide would be effective only against pests and be harmless to non-pests even if misused, it would be applied precisely to where the pest occurs, it would not move away from the application site, it would disappear once it had provided its intended effect and evolution of resistance in pests would take years or even decades. A good regulatory system ought to encourage such innovation (Mittra *et al*. 2014). However, it is unlikely that current trends in the regulation of synthetic pesticides will lead to such as system (Shaner and Beckie 2014).

Improvements to the mode-of-action and formulation of synthetic pesticides, genetic engineering of crops, and newer techniques such as RNA-interference (RNAi), synthetic biology and gene editing, put many of the attributes of the ideal crop protection product within reach. However, regulation of research, and proposed regulation of products of that research, is restricting innovation based on these methods (Tait and Barker 2011). Hence, regulation designed to reduce risk may increase risk by delaying or preventing the introduction of products that are less hazardous and persistent than those they would replace.

A similar story may be told in the seeds industry. Society increasingly demands a reliable supply of nutritious food produced according to high ethical standards. These demands must be fulfilled without using more land, water or energy than at present, and in the face of predicted changes to the world's climate and human population, while providing profitable business for farmers and supporting rural economies. Crops produced by new breeding techniques offer solutions to some of the problems raised by these demands (Godfray et al. 2010), and GE crops are already contributing to the environmental and economic sustainability of farming (Brookes and Barfoot 2017a, 2017b). However, as in crop protection, regulation, particularly if based on current methods for regulating GE crops, may stifle the required innovation (Raybould and Poppy 2012; Smyth 2017).

In this article, I examine the relationship between societal demands of its food production systems and the sometimes vehement opposition to use of technology that has great potential to meet such demands. I first look at why new technologies are needed in R&D in the crop-protection and industry. I then look at problems that arise in attempting to regulate the use of products of new technology and the effects that these problems on our industry's ability to provide useful new products. Finally, I examine how current regulation of new technology should evolve to encourage rather than oppose innovation, and what the role of industry should be in this process. I suggest that industry needs to change from emphasising regulatory compliance and the dire consequences if products of new technology are not used, to offering a compelling vision of how new technology will help society to design agricultural systems that retain the benefits of intensive production while eliminating the effects that are profoundly disliked by many people.

The need for technological innovation in agriculture

After the Second World War, agricultural policy in many parts of the world led to the development of "industrial" farming systems for producing food. Use of mechanisation, synthetic fertilisers and pesticides, irrigation and modern crop varieties led to an almost doubling of world food production – measured as the yield of cereals, coarse grains and root crops – between 1961 and 1996 (Tilman 1999). These production methods also led to environmental problems, including loss of biodiversity, pollution of soil, water and air, soil erosion and unsustainable use of water (Horrigan *et al*. 2002). The diets of many people in developing countries were improved during this period (Evenson and Gollin 2003), while some aspects of diet, for example the greater consumption of fats implicated in causing chronic disease, may have worsened in developed countries (Horrigan *et al*. 2002). These benefits and harms are still relevant today (Bardgett and Gibson 2017).

Deciding whether the results of agricultural policies over the last 70 years have on balance been good or bad is fearsomely complicated. First, one must define good and bad. Secondly, one must choose what changes to include in the analysis; this difficult because agriculture is so widespread and food is so fundamental to human existence that agricultural policy could be implicated in virtually any environmental or societal change. Then, one must compare actual changes wrought by agriculture with the counterfactual of predicted changes that would have happened under different policies (*e.g.*, Evenson and Gollin 2003; Stevenson *et al*. 2013). Finally, one must find a way to value disparate consequences in ways that allow direct comparison. How, for example, should one weigh improvements to human nutrition against loss of biodiversity?

The difficulty in deciding with hindsight whether post-war agricultural policies were good or bad illustrates a fundamental aspect of solving problems: all solutions have unforeseen consequences that produce new problems. That problems are unforeseen in some respects makes decision-making easier than analysing the consequences of a decision. If agricultural policymakers in the 1940s and 1950s knew what we know now about the disparate consequences of industrial agriculture, their ability to make decisions would have been overwhelmed by complexity

Because of unforeseen consequences, knowing that one has made the correct decision – the one that best achieves one's objectives and has fewest harmful side-effects – is often impossible. In such circumstances, the rational objective ought to be to react effectively to change and minimise the unexpected harms and maximise the unexpected benefits of whatever decision we make (Miller 2003). A glib reason, then, for justifying the development of new technology is that we may need it in order to solve the problems caused by older technology. Indeed, opponents of the use technology in agriculture have argued that problems of food security are best solved by changes in economic and social policies because “technological fixes” are temporary and create a vicious circle: use of technology begets problems that lead to the use of more technology to try to solve them, thereby creating bigger problems and more use of technology (Pavone *et al.* 2011; Scott 2011). This argument is regularly applied against the development of new pesticides to overcome the resistance of pests to older pesticides, and has been dubbed “the pesticide treadmill” (Nicholls and Altieri 1997).

Critics imply that using agricultural technology worsens situations by delaying removal of the ultimate social and economic causes of food insecurity. This view seems mistaken on philosophical and humanitarian grounds. First, social and economic change is just as likely as the use of technology to produce unforeseen harmful effects. Secondly, there is no sharp distinction between socioeconomics and technology use. It is difficult to envisage relevant policy change that would not require use of technology in its implementation, just as it is difficult to think of uses of technology that have no socioeconomic implications. Finally, rather than making problems worse by postponing social or economic solutions, using technology may improve matters by alleviating immediate suffering that could otherwise force politicians' hands to adopt measures with longer term negative consequences (see Chapter X in this volume). In essence, improved technology can buy time while social and political improvements are considered.

The case for the continued development and use of agricultural technology is not an argument for technology per se, or a denial of the political, social and moral nature of human problems, as some critics claim (Marx 1983; Pavone *et al*. 2011). It is an argument that new agricultural technology is likely to be necessary in order to achieve the moral and ethical objective of feeding 9–10 billion people adequately in a manner that is socially, economically and environmentally acceptable. In addition, following Miller (2003), we must recognise that the successful use of new technology to solve problems in agriculture has inevitably created new problems. Using new technology to solve these problems does not imply that we are on a technology treadmill, merely that there are no perfect solutions to complicated problems.

It is convenient to portray developers of agricultural technology as regarding the provision of sufficient food as a purely technical problem because it allows opponents of technology to avoid describing the consequences of other options. Indeed, opponents of agricultural technologies seem to fall into a trap that mirrors the one they the one they describe: problems are not political, social and moral, but are the result of technology and could be solved by using less technology – what could be described as an “anti-technological fix” (Raybould and Poppy 2012).

Opportunities for regulated technologies in crop protection and plant breeding

There is a wide variety of new technologies that could lead to improvements in crop production. Of particular current interest is the use of big data and drones and other robotics in “precision agriculture”: precise seed sowing and timely, accurate application of fertilisers, pesticides and other inputs in the smallest amounts for efficacy (Wolfert *et al*. 2017; King 2017; van Evert *et al*. 2017). These developments should not only increase crop productivity, cut pollution, reduce unwanted environmental impacts, reduce the amount of land required to produce enough food, but also save energy by reducing application and production of energy intensive nitrogen fertilisers. Also, advances in nucleic acid sequencing and genetic analysis will increase the speed of conventional plant breeding and broaden the range of phenotypes that breeders are able to produce (Varshney *et al*. 2016). While products of these technologies would have to comply with relevant laws and standards in the countries where they are used, they are unlikely to need specific regulatory approvals of the kind that are required currently for crop-protection products and GE seeds.

Despite the undoubted potential of these unregulated technologies, innovation of regulated products for crop production is still being undertaken and is likely to continue for many years. Pesticides and GE crops will continue to be regulated, and it is likely that the products of at least some new plant-breeding techniques (NBTs), such as gene editing, will also be regulated (Wolt *et al*. 2016). Here, I will briefly summarise the kinds of products that R&D in pesticides, GE crops and NBTs may produce in the next few years.

A fundamental objective of R&D in crop production is to increase the productivity of individual plants. One way to achieve this is by increasing the yield potential of crops by genetically engineering photosynthesis to be more efficient. Increasing the efficiency of photosynthetic enzymes and changing plant architecture so that more sunlight reaches lower leaves are among the strategies being explored (Long *et al*. 2015; see Chapter Y). Innovation in chemicals that alter plant growth will also help to improve the efficiency of photosynthesis in crops; nanoparticles are one line of research in this field (Tripathi *et al*. 2016).

Another important aim of plant breeding is to increase the tolerance of crops to abiotic stressors, such as flood, drought, high temperatures and salinity (See Chapter Z). The ability of crops to cope with these conditions will become increasingly important as the climate changes and water for agriculture becomes scarcer. Various genetic engineering approaches to increasing stress tolerance have been used. Most involve the addition of one or a few genes that lead to the production of sugars or proteins that protect plant cells under conditions that would otherwise cause cellular damage and kill or severely damage the crop. However, these relatively simple approaches often lead to adverse effects to the plant's phenotype owing to side-effects on metabolic pathways that control plant growth and development. More sophisticated synthetic biology approaches will allow engineering of whole metabolic pathways to improve stress tolerance without adversely affecting pathways that control plant growth and development (Cabello et al. 2014). Similar results may be obtained by treating crops with chemicals that prime them to activate faster and stronger protection mechanisms when growth conditions become unfavourable (Savvides *et al*. 2016).

Genetic engineering and NBTs may also contribute to precision agriculture. Improving nitrogen-use efficiency of crops is of particular interest in order to save energy and reduce pollution from ineffective application of nitrogen fertiliser (Galloway 1998). Numerous genes have been suggested as targets for modification, including those controlling nitrogen uptake, assimilation, amino acid biosynthesis and plant senescence (McAllister *et al*. 2012). Genetic engineering of root architecture also has potential to improve nitrogen-use efficiency. Many other traits are also possible through changing root architecture, including increased water-use efficiency and nutrient uptake, and better interactions with soil microbes (Meister *et al*. 2014).

Regulated technologies will continue to be vital in protecting crops from pests and disease by developing products that are applied in small amounts, do not persist in the environment or in crops, and have fewer adverse effects on species that are not pests. Genetic engineering has already contributed significantly to these aims through the development of maize and cotton that produce insecticidal proteins derived from the soil bacterium *Bacillus thuringiensis* (*Bt*). *Bt* toxins have narrow spectrums of activity, providing effective control of insect pests while leaving other organisms unharmed (Romeis *et al*. 2006). The toxins are produced precisely where they are needed – in tissues of the crop – and they tend not to persist and accumulate in soil even after several years of continuous cultivation of a *Bt* crop (Gruber *et al*. 2012). Following their first commercial use in 1996, *Bt* crops have provided numerous economic and environmental benefits, including reduced use of broad-spectrum pesticides (Brookes and Barfoot 2017a, 2017b).

R&D continues on the genetic engineering of insecticidal proteins in crops. Maize and cotton that produce more than one *Bt* toxin are in commercial use and provide better pest control and insect-resistance management. New *Bt* proteins produced by protein engineering, along with anti-feedant proteins such as lectins, will extend the options for combining insecticidal proteins in GE crops (Lombardo *et al*. 2016). Another trend is expanding the range of crops protected by *Bt* toxins; for example *Bt* brinjal (eggplant or *aubergine*) is commercialised in Bangladesh, and commercial trials of *Bt* cowpea are in progress in Nigeria (Hallerman and Grabau 2016).

RNA-interference (RNAi) is another mechanism for controlling pests. It uses gene sequence data to design double-stranded RNA (dsRNA) molecules that shutdown expression of a gene that is specific to a target pest, providing control of the pest with, in theory, no adverse effects on other species (Bachman *et al*. 2016). GE crops producing both dsRNA and *Bt* proteins for corn rootworm control are in development and near to commercialisation (Head *et al*. 2017). NBTs are expected to provide further mechanisms for insect control for introducing into crops; in particular they enable precise manipulation of plant secondary metabolism to enhance crops' innate resistance to insects (Jirschitzka *et al*. 2013).

GE virus-resistant squash and papaya have been in commercial use since the late 1990s, and control of viral disease continues to be a fruitful area for GE crop R&D (Lindbo and Falk 2017). Commercial deployment of GE crops resistant to fungal or bacterial diseases has lagged behind that of GE virus resistance, often because of regulatory delays (Mullins 2015). However, GE potatoes resistant to late blight are nearing the market (Guenthner 2017), and several potential products are showing promise in field trials; these include oranges resistant to the bacterial disease citrus greening (Dutt *et al*. 2015) and bananas resistant to *Xanthomonas* wilt (Tripathi *et al*. 2014).

GE herbicide-tolerant (HT) crops have been in commercial use for about 20 years and, like insect-tolerant crops, have provided economic and environmental benefits centred on fewer applications of herbicides and simplifying no-till cultivation (Brookes and Barfoot 2017a, 2017b). R&D trends are also similar: newer GEHT crops are tolerant of more than one herbicide, which should slow the evolution herbicide-resistant weeds (Green 2017). Gene editing provides a powerful means to alter enzymes that are the targets of herbicides, thereby offering new methods to create herbicide-tolerant crops (Lombardo *et al*. 2016). RNAi may also be useful in weed management, although in this case dsRNA is likely to be sprayed on to plants, particularly herbicide-resistant weeds, in order to change their sensitivity to herbicides (Green 2014).

In addition to plant breeding for pest control, research continues into crop protection products that act or can be applied more precisely. "Traditional" synthetic chemistry will continue to be vital for managing many pests and diseases. New pesticide modes of action are still being developed and commercialised (Jeschke 2016) and are crucial to slowing the evolution of resistance to pesticides. Molecules with new modes of action tend to be discovered by screening large libraries of synthesised compounds; however, natural products – metabolites produced in living cells – are also an importance source.

Once an interesting molecule is discovered, hypothesis-led redesign is undertaken to improve properties such as its potency, stability, and uptake by and mobility within plants (Loso et al. 2017). Advances in reducing non-target toxicity, especially to people, while maintaining or increasing potency against the target pest, have been the key to successful development of many recent new products (Wing 2017). In general, the greater complexity of natural products makes their redesign more difficult and time-consuming than that for chemically synthesised molecules (Sparks et al. 2017).

Biological pesticides are likely to increase in importance in crop protection owing to societal concerns about overuse of chemical pesticides and regulatory reaction – perhaps over-reaction – to these concerns (Balog et al. 2017). As Glare (2015) points out, the main aim of defining a pesticide as biological is to indicate lower mammalian toxicity and reduced risk to non-target organisms compared with synthetic pesticides. However, it is wrong to assume that a biological origin is a guarantee of safety.

Regulatory definitions of biological pesticides usually include viruses, bacteria and fungi that are used to suppress pest populations. Suppression may arise through toxicity or competitive inhibition. Semiochemicals, which modify pest behaviour, are also usually regarded as biological pesticides for regulatory purposes. In biological pesticides based on bacteria or fungi, the organisms may be used while living or dead. Formulations of *B. thuringiensis* that make use of its various insecticidal proteins to control important agricultural, forestry and public health pests use live bacteria. Products that use GE bacteria to produce dsRNA with activity against pests will use heat-killed bacteria (e.g., Zhu et al. 2011). The regulatory position of the latter products is uncertain and they may be considered as GE organisms rather than as biological pesticides.

A final method worthy of consideration for innovation in crop protection is nanotechnology. Nanomaterials offer new formulations that can deliver crop protection chemicals more accurately and precisely to the target pest. Greater control over the timing of release of a chemical is a particular advantage of nanomaterials (Parisi et al. 2015; Wang et al. 2016). Nanoparticles themselves may be useful as pesticides. Nanoparticles of metal or metal oxides are toxic to a range of bacteria, fungi and plants and could form the basis of new bactericides, fungicides and herbicides (Baker et al. 2017).

Products of regulated technologies will do more than increase or protect crop yield. They have enormous potential to increase the nutritional quality of food. In 2013, Bhutta et al. estimated that worldwide 3.1 million children under 5 years old die annually as the result of malnutrition; this represents about 45% of deaths in this age group. Genetic engineering of crops has great potential to help cut this terrible loss of life. A review by De Steur et al. in 2015 summarised research into fortifying crops with micronutrients: target nutrients include vitamins A, B9, C and E, copper, iron and zinc; target crops include rice, maize, wheat, barley, sorghum, cassava, oilseeds, potatoes and various vegetables. Crops intended to reduce vitamin A deficiency are perhaps the most advanced, and include the well-known example of Golden Rice and also sorghum, banana and cassava. None of these crops is commercialised, owing in part to regulatory barriers; however, small-scale clinical trials of food from these crops and the beneficial effects of conventionally bred biofortified crops suggest that were these crops to receive regulatory approvals, they could be an effective source of micronutrients to help prevent malnutrition (De Steur et al. 2017).

GE crops that improve human or livestock nutrition through altered fat content are already commercialised. Plenish® soybeans that contain zero *trans* fat and high amounts of monounsaturated fat have been available since 2014. Applications to sell other GE soybean and oilseed rape varieties with modified fatty acid profiles are undergoing regulatory reviews. Numerous other GE crops intended to have human-health benefits are in development, and include tomatoes enriched with anthocyanins, pineapples with high lycopene content and gluten-free wheat (Glass and Fanzo 2017). Development of GE crops for animal feed concentrates on increasing nutrients, such as lysine, or decreasing anti-nutrients, such as lignin and phytate (Tillie et al. 2013).

Finally, regulated products also play a role in reducing food waste. Synthetic pesticides have long been used to prevent spoilage of stored agricultural products (Hagstrum and Phillips 2017). One of the first GE crops to be commercialised was the Flavr Savr™ tomato, in which pectin solubilisation was decreased, leading to ripe fruit that had improved flavour and longer shelf-life (Kramer and Redenbaugh 1994). Recently, non-browning GE Arctic® apples and GE Innate™ potatoes have been commercialised. Both products reduce waste during processing and the apples enable fresh slices to be sold directly to the consumer (Glass and Fanzo 2013).

The above discussion shows that regulated technology has the potential to deliver improvements in crop production and human and animal nutrition. A key to realising this potential is that regulatory barriers do not stifle the development and commercialisation of innovative products. To avoid such a result, advocates of the use of technology in agriculture will need to present a better case for its benefits than hitherto; in short, the use of technology must offer more than just greater efficiency of industrial agriculture. The rest of the article will examine the regulation of new technology and discuss how a case for widespread societal benefits of applying such technology to agriculture could be made.

Regulation of new technologies in crop protection and seeds

Tait (2007) categorised innovation in life sciences according to the effect that new technologies and their products have on the companies and industries that produce them. Incremental, or path-dependent, innovation improves existing products or services and is easily accommodated within existing business models and regulatory systems. Disruptive, or path-breaking, innovation, on the other hand, leads to major shifts in the types of product offered and may create completely new industries. Such innovation may require new types of regulation.

In general, innovation in crop protection has been regarded as incremental, and this is likely to be true for many of the potential products described above. Incremental innovation does not require the passing of legislation to create new categories of regulation or radical overhaul of existing regulatory methods. This does not mean that regulations are simple or unchanging, rather the legal and scientific conceptual frameworks that support them are relatively stable. Hence, while achieving worldwide registrations of a crop-protection product is complicated because of different requirements among countries, and regulatory decision-making is becoming more conservative in many countries (Handford et al. 2015), each new pesticide will be treated fairly similarly to its immediate predecessor in terms of data that must be supplied and the analysis of those data to assess risk. This is true even of synthetic pesticides that incorporate nanotechnology (Amenta et al. 2015).

Genetic engineering of crops was regarded as a disruptive technology requiring new regulation in some countries. Mittra et al. (2011) point out that it was not inevitable that GE crops would be developed and marketed mainly by large agrochemical firms; the technology and products could have been developed by seed of food companies. If the products had been developed by seed companies, they may have been regarded as an incremental innovation in the seeds industry. However, their development by agrochemical companies led to their being regarded as disruptive innovation in the agrochemical industry and, as a consequence, regulations tended to be based on those governing pesticides rather than seeds.

Had GE crops been regarded as an incremental innovation in the seeds industry, their regulation may have concentrated principally on matters related to plant breeders' rights (see introduction). However, as they were perceived as a disruptive innovation in the agrochemical industry, the focus of regulation was risk to human and animal health and the environment. The United States adapted existing legislation and used existing agencies to regulate GE crops: the Food and Drug Administration evaluated risks to the food and feed supply; the Environmental Protection Agency evaluated GE crops that control pests (e.g., *Bt* crops); and the Department of Agriculture evaluated risks to agriculture by regarding GE crops as potential plant pests (McHugen and Smyth 2008). Most other jurisdictions created new agencies and regulations with the specific purpose of regulating GE crops (Evenson and Santaniello 2004).

Developing new regulations rather than adapting old ones created problems that still dog the commercialisation of GE crops: long and uncertain regulatory decision-making and public scepticism about the safety and benefits of the technology and the motives of the industry that uses it (Johnson et al. 2007). The problems are more serious in some countries than others and to an extent have lessened as policy-makers and regulators become more familiar with GE crops. However, these problems still cause serious problems in the European Union (EU) and countries, such as many in Africa, with regulatory systems that are influenced by the EU (Paarlberg 2010). I briefly review these problems from the perspective of an applicant trying to guide a product through the system.

The major problem with new regulations for GE crops may be summed up by the term “risk assessment – policy gap”, which was coined by Evans et al. (2006) to describe a situation where policy objectives are unclear and risk assessors have to interpret them before they can begin a regulatory risk assessment. GE crop regulations are often long on what data must be submitted to the relevant authorities, but are usually vague about what risks should be assessed and how the data will be used to make decisions. This means that applicants have to infer what decision-makers would regard as a harmful effect of growing or importing a GE crop, and use the data that they are required to collect in order to test hypotheses about the likelihood that use of their particular product causing such harm.

Such a situation creates serious difficulties. First, the focus on data creates a pedantic, legalistic approach where the minutiae of study design and the completeness of a data package are more important than whether hypotheses that are relevant to decision-making have been tested sufficiently. Studies may have to be repeated because of scientifically trivial deviations from guidelines; studies may have to be larger or more complicated than is scientifically necessary in order to meet the different data requirements among countries; and studies may be conducted even though they test no relevant hypothesis, or test a relevant hypothesis with no greater rigour than do existing studies (Raybould 2006). Such work can be extremely wasteful of time, effort and money, especially where data requirements change continually without any obvious benefit for decision-making (Raybould and Poppy 2012).

A second problem is that divorcing risk assessment from clear policy objectives creates the prefect opportunity for delaying decision-making and for creating policy *ad hoc* under the influence of vociferous opponents of GE crops. If risk assessment is seen solely as an exercise in reducing scientific uncertainty about the properties and likely behaviour of the GE crop, then it can be continued indefinitely. Empirical hypotheses can never be proved, hence uncertainty is always with us, and claiming a need to reduce scientific uncertainty can be used to justify endless further studies before a decision is possible. It follows that decisions can be delayed indefinitely or made suddenly for arbitrary reasons. This is the current situation in the EU (Davison and Ammann 2017).

Where a regulatory system is failing to make timely decisions because of a risk assessment – policy gap, defining policy, not conducting more scientific studies, should be the priority for fixing the problem. Ironically, in calling for risk assessment to be “science-based”, advocates of genetic engineering for crop improvement actually play into their opponents hands by amplifying the importance of scientific uncertainty over policy uncertainty. The emphasis on scientific uncertainty enables opponents of the technology to create diversionary furores about “lack of scientific consensus” and thereby avoid having to address the economic and social consequences of their anti-GE crop policy (see Hilbeck et al. 2015, for example). Proponents of a technology can never win an argument based on scientific certainty about its safety because there can be no such thing. They can, however, win arguments about how using the technology may help to deliver certain policy objectives, and about the malign effects on regulatory systems of an unwillingness to discuss the policy objectives that the systems are supposed to deliver (Raybould 2012). I will return to these matters below when discussing how regulation of new agricultural technologies could be improved.

The consequences of uncertainty about regulatory approvals for importation of GE crops include higher commodity prices and cost of food (Anderson 2010) and restrictions on the choice of seeds products for farmers in countries that export crops to countries where import approvals are delayed (Stein and Rodríguez-Cerezo 2010). Delayed decisions over approvals for cultivation of GE crops harm farmers who are unable to benefit from the reduced input costs associated with some GE crops (Park et al. 2011) or from price competition between chemicals and GE crops that solve similar agricultural products (Graff et al. 2009).

Perhaps the most important consequence of unpredictable regulation is that its cost and complexity have severely limited the opportunities for institutions outside the large multinational companies to commercialise GE crops (Huesing et al. 2016). Solving the complex problems facing agriculture is likely to require innovations from small companies and the public sector to develop products that improve the production of minor and orphan crops (ASSAf 2017). It is important, therefore, that regulation of new technology enables a much wider range of organisations to develop products than has been the case with GE crops. In the next section, I discuss some principles for how this could be achieved.

Improving the regulation of new agricultural technologies

The Organisation for Economic Cooperation and Development (OECD) has set out eight “principles of good regulation” that are a valuable guide to thinking about whether or how new agricultural technologies and their products ought to be regulated (OECD, 2014). Table 1 summarises each principle, along with a comment about its relevance to regulation of GE crops and any new regulations for new agricultural technology. I use the principles to structure a discussion of how current regulations could be improved. I focus on regulations covering GE crops to illustrate the potential pitfalls of regulation, but the remarks are intended to apply to regulatory systems generally.

Table 1. OECD Principles of Regulation (OECD 2014) illustrated with learning from regulation of GE crops

Principle of Regulation	Learning from GE Crops
1. Deliver clear policy goals	Regulations should serve agricultural, environmental and economic policy objectives
2. Have a sound legal and empirical basis	Properties of a product may be a sounder basis for regulation than are its methods of manufacture
3. Produce benefits that justify costs	Concentrate on identifying potential harm and benefit not on administrative compliance and identifying differences

4. Minimise costs and market distortions	Make decisions based on risk and opportunity regardless of how the product was produced
5. Promote innovation	Provide incentives to develop beneficial products not only restrict use of potentially harmful products
6. Be clear, simple and practical for users	Reuse data where possible: data on similar products and data on same product from different country
7. Be consistent with other regulations and policies	A precautionary approach to agricultural technology may clash with economic policy
8. Be compatible with competition and trade	Minimise asynchrony between regulatory decisions in multiple countries

As noted above, a major problem concerning regulation of GE crops has been the existence of a risk assessment – policy gap (violation of OECD Principle 1). Often the purpose of regulation is obscure; while there may be a stated intention to protect the environment and human and animal health, this is insufficiently precise for good regulation. One reason is that the exact nature of harmful effects that the regulations seek to control needs to be clear. In the case of human and animal health, harmful effects are usually unambiguous and uncontroversial, namely increased mortality and morbidity. On the other hand, agreeing what is to be regarded as environmental harm can be difficult, particularly at a landscape scale where individual preferences about aesthetics may play a large part in whether someone regards a particular effect as harmful (Sanvido et al, 2012, van Zanten et al. 2016).

A second reason for policy obscurity relates to the acceptability of risk. Acceptable risk is a tricky term to define and requires numerous policy decisions (Table 2). Risk comprises two elements: the severity of a harmful effect that may result from an activity, and the likelihood that the effect will occur. In principle, the likelihood of an effect is a matter for science, whereas determining its severity is ultimately a question of policy.[2] Even when people agree on what constitutes a harmful effect, they may disagree about how to judge its severity and how to weight severity and likelihood in determining the amount of risk. Determining whether a tiny probability of a serious effect is poses greater risk than a high probability of a minor effect requires potentially difficult judgement of contrary opinions rather than simply making a scientific calculation.

Table 2. Terms that need to be determined in order to define acceptable risk

Property of an activity	How determined
Harm caused	Policy decision

[2] The magnitude of an effect is in principle a matter solely for science. However, deciding severity involves judging the importance of an effect of a particular magnitude. Severity is separate from acceptability; agreement that an activity poses a certain severity of risk, does not imply agreement about whether the risk is acceptable.

Severity of harm	Policy decision
Likelihood of harm	Scientific calculation
Amount of risk **(= severity and likelihood of harm)**	Policy decision
Benefit resulting	Policy decision
Value of benefit	Policy decision
Likelihood of benefit	Scientific calculation
Opportunity **(= value and likelihood of benefit)**	Policy decision
Method of weighting risk vs opportunity **(Ethical vs utilitarian)**	Policy decision
Acceptability of risk **(Opportunity > risk if utilitarian)** **(Risk < threshold if ethical)**	Policy decision

An additional difficulty in defining acceptable risk is how to make trade-offs with the opportunities of the activity in question. Opportunity is the opposite of risk, and comprises the value of the benefits that may ensue from an activity, and the likelihood of those benefits arising. Like risk, it comprises policy and scientific elements. Policy defines the beneficial effects of an activity and the value to be placed on benefits of a certain size, and science determines the likelihood of those effects arising as a result of the activity.

In essence, there are two methods of handling trade-offs between risk and opportunity. Ethical decision-making sets a threshold for acceptable risk, and if the risk of a proposed activity exceeds this threshold, the activity will not be permitted regardless of the opportunity. If there are many options for decision-makers, they can choose among those that are below the risk threshold, perhaps on the basis of which provides the most opportunity. Utilitarian decision-making, on the other hand, considers the net opportunity (the opportunity minus the risk) for each option and chooses the option with the highest ne opportunity. This option could be most risky but also provides the largest opportunity (Sanvido et al. 2012).

A key point from the above discussion is that when considering introduction of regulation of new technology, it is crucial that, as far as possible, the policy objectives are considered first. The regulations can then be designed to deliver those objectives. Too often regulatory decision-making over GE crops seems to become bogged down because in the absence of clear policy objectives, the regulatory system has to try to create them.

Regulatory systems seeking to create policy may be the source of regular complaints that decision-making over GE crops is politicised (e.g., Smyth and Phillips 2014). For reasons described above, it is essential that politics be involved in crafting regulation: the opportunities to be sought, the risks to be controlled and how opportunity and risk are balanced are matters of public policy. However, these policy decisions should be taken *ex ante* in order to design good regulation; regulation should not be used to work out policy.

Just as regulation of new technology should not be used to resolve policy, it should also not be a vehicle for scientific research. Regulation should be based on sufficient scientific knowledge of the relevant technology, not be the means of producing that knowledge (Hill and Sendashonga 2003).

At the beginning of the translation of scientific discoveries into new technology there may be high uncertainty about the kinds and properties of products that may be produced by the technology (Tait et al. 2017). In order to inform policy that may lead to regulation of such products, it is likely that scientific research will be necessary to characterise what products the technology could produce, and to predict the behaviour of those products. Of particular interest will be the potential for unintended and unwanted side-effects of potential products. While this being is determined, it may be necessary to regulate research in order to minimise risk to scientists undertaking it, and risks to the wider public. Once sufficient knowledge has been gained to inform policymaking, thoughts can turn to regulation of products of the technology, along with any revision of regulation of the basic research (Raybould et al. 2012).

The first conclusion to be drawn from scientific research is whether products of the technology should be regulated, and, if they should, whether existing regulations are suitable. There is much discussion currently about the regulatory status of gene-edited crops, which centres on their similarity to conventional or GE crops. Many scientists argue that gene-edited crops should not require regulation if they are indistinguishable from products of conventional breeding, and any regulation should cover only products that are significantly different from those produced by conventional breeding. Regulation should not cover gene editing itself (Caroll et al. 2016, Huang et al. 2016). These recommendations are in line with OECD Principles 2, 3, 4, 5 and 7, and could be implemented in a similar fashion to Canadian regulation of GE crops. Others argue that gene-edited crops should be regulated as GE crops because similar processes are used in their creation (reviewed by Wolt et al. 2016). Again, this view could be consistent with OECD Principles 2 and 7, perhaps depending on whether the “legal” or “empirical” basis for regulation (OECD Principle 2) is regarded as stronger. It is difficult to envisage process-based regulation of GE crops fulfilling OECD Principles 4 and 5.

If products of a technology are to be regulated, it is important to differentiate between studies that are useful for formulating regulatory policy about a technology and those to be required for regulatory decisions about individual products of that technology. Many studies required for regulatory risk assessments of GE crops are more like basic research into whether genetic engineering produces unintended effects, rather than studies that focus on unintended side-effects of the new trait introduced by the genetic engineering.

When seeking approval for import or cultivation of a particular GE crop, applicants have to submit a compositional analysis study: a detailed comparison of the proximates (protein, fat, carbohydrate etc.), minerals, vitamins, fatty acids and anti-nutrients of the GE crop and a genetically similar conventional variety. A similar phenotypic characterisation study is also required; this compares the gross phenotypes of the GE crop and a genetically similar non-GE comparator (see Raybould et al. [2010] for variables that are typically measured in these studies). The origin of these studies is probably a concern that genetic engineering would have unpredictable effects on crop phenotypes. This concern is understandable, but leads to serious problems. Compositional analysis and phenotypic characterisation studies are expensive to produce and time-consuming to review, but contribute little to risk assessment, thereby violating OECD Principle 3. In addition, regulatory authorities often require studies to be performed on material grown in their country or to their own particular design, or both, thereby violating OECD Principle 6.

The reason that these studies contribute little to risk assessment is that potentially harmful differences are rarely, if ever, defined (e.g., a 50% reduction in nutrient X or a 50% increase in anti-nutrient Y). Hence, the studies are simply tests of the null hypothesis of no difference between the GE crop and the comparator, rather than a test of the hypothesis that use of the GE crop will not be harmful. Extensive cataloguing of differences may feel like a thorough assessment of risk, but it may have the unintended effect of increasing risk because a potentially harmful difference may be missed among a mass of data of unknown relevance. This criticism would apply equally to omics techniques that profile genetic or metabolic differences and which are suggested as means to “improve” risk assessment for regulated products in agriculture (Li et al. 2017).

Phenotypic and compositional analyses of GE crops teach us valuable lessons for the regulation of products of new agricultural technologies. First, studies that may provide evidence to test hypotheses about techniques should be avoided in risk assessments for products. Testing hypotheses about the relative variability of products created by different methods may provide useful knowledge to set regulatory policy; however, for risk assessment, we need to specify precisely what changes we regard as indicating potential harm. Second, data requirements need to be reviewed regularly. The many compositional and phenotypic analyses conducted for product registrations may be viewed collectively as robust corroboration of the hypothesis that genetic engineering per se does not introduce harmful unintended changes into crops more frequently than does conventional breeding (although genetic engineering could introduce traits that have unwanted consequences, as could conventional breeding). Hence, there is a strong argument for no longer requiring such studies for GE crops in which the introduced trait is not intended to change metabolism (Herman and Price 2013). Even for crops with altered metabolism, a hypothesis-driven approach that searches for specified potentially harmful changes would be more useful than profiling.

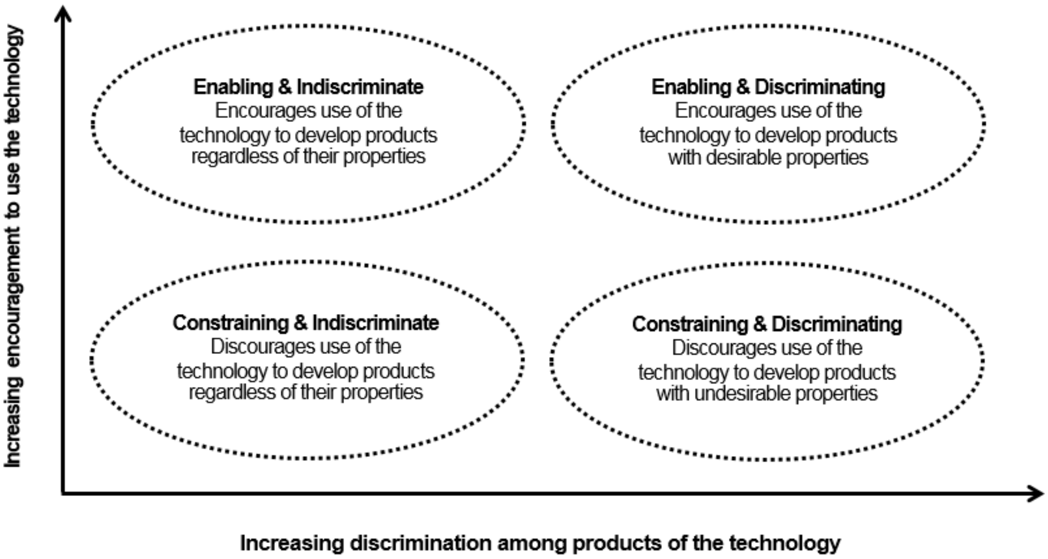
As with reducing policy uncertainty, spending time reducing scientific uncertainty before introducing product regulation is likely to speed up commercialisation of products. Just as many of the delays in GE crop decision-making result from the regulatory system trying to sort out policy, much of the expense and time in producing regulatory dossiers comes from conducting studies that assess the technology not the product. While developers may want rapid introduction of regulation of products of new technology, carrying policy and scientific uncertainties about the technology into product regulations could be disastrous. A pause to clarify policy and conduct research in order to produce effective regulations may save much time in the long run.

Two final points about GE crops and regulation of future new technologies. Regulation of GE crops seems generally lacking in encouragement for innovation (violating OECD Principle 5), even in jurisdictions where the stated economic policy is growth based on exploiting new biological knowledge (violating OECD Principle 7) (Masip et al. 2013). Indeed, Miller and Conko (2004) argue that some companies colluded in making GE regulations restrict innovation in order to discourage new competitors and protect themselves from the dynamism of the market.

Chataway et al. (2006) describe various approaches to regulation: enabling verses constraining, and discriminate verses indiscriminate. These opposing approaches combine to give four types of regulation (Figure 1). The ideal combination for encouraging innovative use of a new technology is probably enabling and discriminating, whereby policy encourages use of the technology to develop products with desirable properties. Too often regulation of GE crops appears constraining and indiscriminate and institutions are simply discouraged from developing any kind of GE crop.

Defining what is desirable may be controversial. It will involve difficult policy decisions (Table 2) as no class product is universally desirable; even potentially life-saving drugs with few side-effects may not be used because their cost diverts money away from interventions that could save more lives (Eichler et al. 2015). However, shirking such decisions will lead to regulation that discourages innovation, or at least innovation that is beneficial to society. I return to this subject in the next section.

Figure 1. Approaches to the regulation of products of a new technology. The definitions of the types of regulatory system (in bold) are from Chataway et al. 2006)



The only OECD Principle not mentioned so far is 8 – compatibility with trade and competition. Asynchrony of cultivation and import approvals has caused severe problems for the commercialisation of GE crops (de Faria and Wieck 2015). One contributor to asynchronous approvals is lack of internationally accepted standards for certain regulatory studies, particularly field trials (Garcia-Alonso et al. 2014). Greater mutual acceptance of data produced in different countries would not only help to reduce the costs and complexity of regulation (fulfilling OECD Principles 3 and 6), but would also help to coordinate regulatory decision-making among countries. Greater use of existing data produced elsewhere does not mean that countries are forced to make similar regulatory decisions. Given that policy objectives are the driver for decision-making (Table 2), it is entirely feasible for countries to make different decisions based on the same data.

In summary, regulation of products of new agricultural technologies can improve greatly on current regulation of GE crops. Good regulations follow from clarity about policy objectives and sufficient scientific knowledge about the technology. Product regulation must not be used to make policy or carry out scientific research. A delay in introducing product regulation in order to clarify policy and conduct essential research should be regarded as a good investment of time. Perhaps the most important lesson is that politics[3] is essential for good regulation. Removing politics from the formulation of regulations will almost guarantee a system that fails to make timely decisions because the decision-making will have to create policy rather than execute it.

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[3] Meaning politics as the methods for setting public policy; not party politics.

Societal acceptance versus regulatory approval

Regulatory approvals for products of a particular technology do not ensure that the technology is welcomed by society. Product regulation cannot cover every aspect of how a product is used. In particular, it hard to predict how the introduction of new products will alter economic and social behaviour at large scales. While regulation of crop protection and seeds products can minimise risk to human and animal health, and to the local environment where they are used, it cannot control how the products contribute to the development of farming systems. Hence, although people may accept that use of certain products of an agricultural technology are "safe" in terms of meeting regulatory requirements in toxicology and environmental fate, they may be reluctant to accept the use of the technology in general owing to dislike of industrial agriculture that it is perceived to encourage. Hence, stressing that its products meet regulatory standards is often an inadequate response to opposition to a technology, and may lead to more restrictions as regulation tries to catch up with public opinion (Malyska et al. 2016).

There are many critiques of industrial agriculture that centre on technical analysis of its economic inefficiency or its ecological unsustainability. However, another common theme is yearning for farming as it used to be, or at least as it was imagined to be: the loss of faming as creator of beautiful landscapes; and the loss of farming as local businesses, rooted in rural life, that provided food of known provenance. This loss was captured by Manning (2004) in an essay in which he called industrial agriculture a "malign force":

> "… food experts now speak not of food but of commodities. And with reason. The produce of farm fields is no longer a diverse flow of foods to tables so much as inputs to a series of factories. Livestock have left the farm and are now produced in what are called "confinement operations, beastly concentration camps where chickens, hogs, cattle and turkeys are packed and fed a stream of grain."

While product developers can stress, with good reason, the lower mammalian toxicity and environmental persistence of crop-protection products that new technology helps to provide, there is a widespread perception that products of new technology perpetuate or even worsen the trends the Manning decries. For example, concerns about GE crops further encouraging the industrialisation of agriculture have been around since at least the mid-1990s (Crouch 1995), and Manning himself writes of "gene jockeys" being part of a lobby that benefits from industrialisation of agriculture.

Developers and users of new agricultural technology often portray the views expounded by Manning and others as romantic, and point out the necessity of improving agricultural production in developing countries (e.g., Blancke et al. 2015). Hence, defence of new technology often becomes a caricature of rational use of science to prevent mass starvation and malnutrition fighting to overcome the irrational prejudices of well-fed, hopeless romantics in developed countries. Judging by continuing controversy about GE crops, such arguments are counterproductive.

Discussing the best ways to encourage conservation of biodiversity, Knowlton (2017) wrote,

> "… unrelenting doom and gloom in the absence of solutions is not effective … Social scientists have known for decades that large problems without solutions lead to apathy, not action. Yet much of conservation communication still seems to be focused on scaring people into caring. As a [conservation] community, we seem to be addicted to despair."

She went on explain that, while not being a Pollyanna, she has found that optimistic messages inspire and energise people to find solutions to problems.

Advocates of new technology in agriculture could learn much from Knowlton's short essay. Often communication about new technology in agriculture is doom and gloom and scaring people into caring: in essence, "allow us to use this technology or tens of millions of people will starve." Even if this were true, hopes for farming systems that are less like factories are not irrational or inevitably wrong, and presenting them as so does worse than create apathy; it creates mistrust and hostility.

Currently, feeding 9 billion people may be incompatible with small-scale agriculture selling to local markets. However, advocating the need for industrial agriculture should not necessarily mean defending its every effect; one can accept that something is necessary while hoping and planning for something better. As discussed earlier, the "right decision" is often impossible (Miller 2003) and claiming that industrial agriculture has no flaws is unrealistic, inaccurate and seems defensive. Creating optimism for better farming – retaining the good aspects of industrial agriculture while acknowledging is unpopular features and trying to eliminate them – seems much more likely to lead to acceptance of new technology than does peddling relentless doom and gloom about the future should the technology remain unused.

Knowlton recognised that conservation "is often two steps forward, one step back — or frustratingly, one step forward, two steps back". Using products of new technology in agriculture will be similar. Improvements in the productivity or nutritional quality of crops may sometimes be associated with greater industrialisation, even when this was not the intention. However, it is important that advocates of new technology do not imply that concern about the side-effects of greater productivity is irrational. Even if one thinks that, on balance, the productivity – industrialisation trade-off is worthwhile, listening to those with a different opinion, and showing that you have understood it, ought to create a more optimistic atmosphere for discussing the role of new technology in agriculture.

A final point is that the onus for creating a more optimistic discussion about innovation in agriculture should not rest solely on developers of technology and its products. Recently, Tait et al. (2017) have proposed that public debate about new technology should conform to a Responsible Engagement standard. Among the guidelines for developing a standard they suggest ensuring "equitable treatment across all stakeholders" and not allowing "the values and interests of one stakeholder group to restrict the freedom of choice of others." Of crucial importance is that the standard would require all interested parties to engage responsibly, not just industry.

Conclusion

Using new technology in agriculture has great potential to improve human well-being by leading to the development of products that improve the quantity, quality and reliability of food production. Moreover, there are good grounds for optimism that demands for improved production can be delivered by agricultural systems that also meet increasing ethical and aesthetic standards. The successes of industrial agriculture originate from economies of scale. If miniaturisation of equipment, precision agriculture and gene editing can combine to reduce the scale at which economies are realised, farming systems may become more diverse and less industrial.

Crucial to realising this ambition are regulations that encourage innovation, and give small companies and public sector institutions the opportunity to commercialise their products. In order to achieve this, product regulations must be designed to achieve clear policy objectives and be based on sufficient scientific knowledge. As experience with GE crops shows, product regulation should not be the place to conduct policy debates, nor should assembling data to meet regulatory requirements be redirected to basic research into a new technology. Failure to define clear policy objectives will lead to protracted and capricious decision-making, and using regulations to conduct research will mean requests to submit vast amounts of regulatory data that fail to assist decision-makers. Unpredictable, costly regulation is the enemy of innovation.

Finally, good regulation will be necessary but insufficient to realise the potential of new technology. Social acceptance of products of new technology is also crucial. Key to achieving this is creating more optimistic messages that new agricultural technologies are about more than averting mass starvation. New technology can help to provide sufficient food and promote the social, ethical and aesthetic aspects of farming that people value, but that often disappear as agriculture becomes more industrialised.

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